Antidepressants

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The Symptoms of Depression are

- Feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

Mechanism of Antidepressant Drugs

Potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin (5-HT) in the brain.

Note: The biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters.

Antidepressants

- Typically take at least 2 weeks to produce significant improvement in mood
- Maximum benefit may require up to 12 weeks or more
- Patients who do not respond to one antidepressant may respond to another
- 80% or more will respond to at least one antidepressant drug.

The selective serotonin reuptake inhibitors (SSRIs)
Fluoxetine
Citalopram
Escitalopram
Fluvoxamine
Paroxetine
Sertraline

- Inhibit serotonin reuptake.
- Increased concentrations of the neurotransmitter in the synaptic cleft
- The SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression.

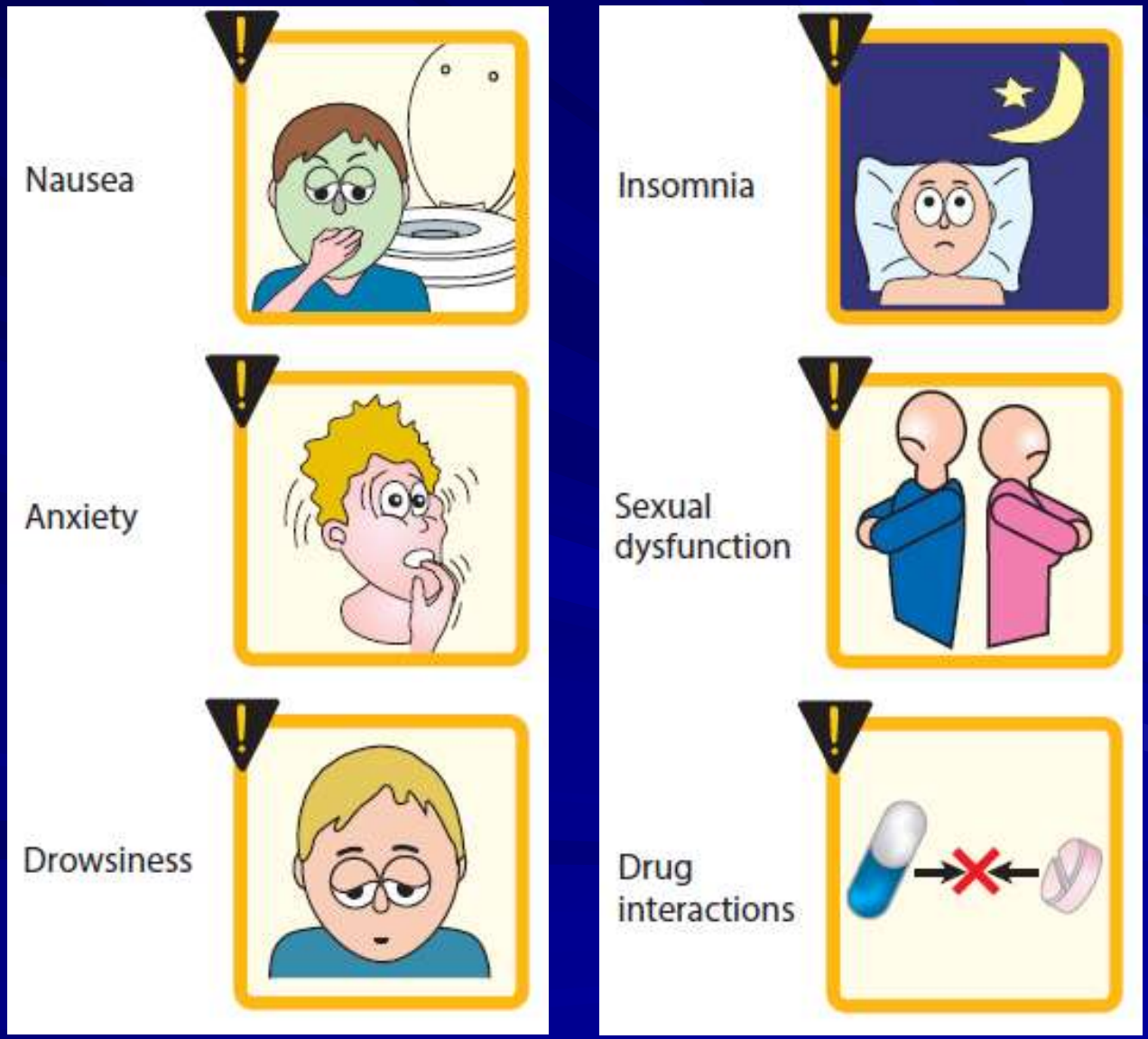
Therapeutic uses of SSRIs

1. The primary indication is depression
2. Obsessive-compulsive disorder
3. Panic disorder
4. Generalized anxiety disorder
5. Posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder
6. Bulimia nervosa (only fluoxetine is approved for bulimia).

Pharmacokinetics

- Well absorbed after oral administration.
- Food has little effect on absorption (except with sertraline, for which food increases its absorption).
- Half-lives range between 16 and 36 hours, fluoxetine having a much longer half-life (50 hours)
- Metabolism by cytochrome p450 & glucuronide or sulfate conjugation
- Fluoxetine and paroxetine are potent inhibitors of a CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, antipsychotic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs.

Adverse effects of selective serotonin reuptake inhibitors.



Adverse Effects of Selective Serotonin Reuptake Inhibitors

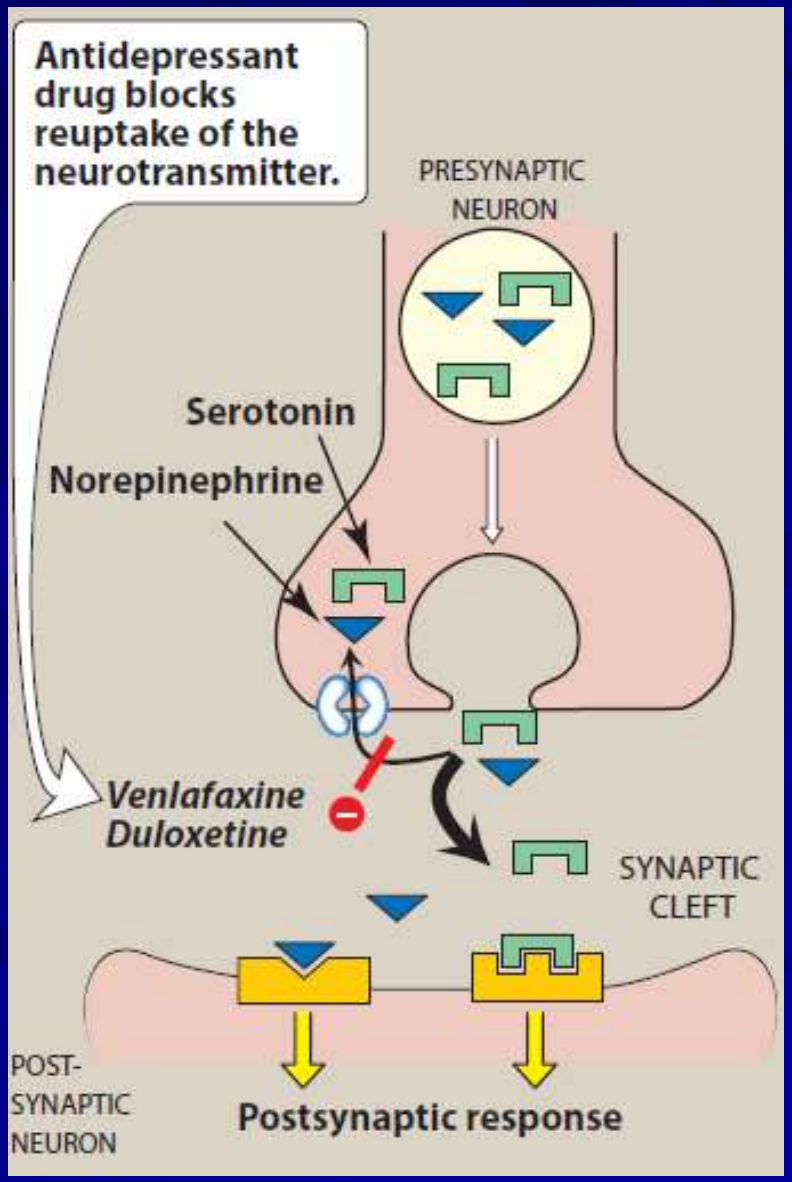
- Headache, sweating, anxiety and agitation,
- Gastrointestinal (GI) effects (nausea, vomiting, diarrhea)
- Weakness& fatigue
- Sexual dysfunction
- Changes in weight
- Sleep disturbances
- Hyponatremia(in the elderly and patients who are volume depleted or taking diuretics)

- Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant.
- Overdose may cause
  - **C**ardiac arrhythmias
  - Seizures
  - Serotonin syndrome (hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status
- Abrupt withdrawal cause headache, malaise, and flu-like symptoms, agitation, irritability, nervousness.

Serotonin/norepinephrine reuptake Inhibitors
SNRIs
Venlafaxine
Desvenlafaxine
Levomilnacipran
Duloxetine

- Inhibit the reuptake of both serotonin and norepinephrine

Proposed mechanism of action of selective serotonin/ norepinephrine reuptake inhibitor antidepressant drugs.



Venlafaxine and Desvenlafaxine

- Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake.
- Desvenlafaxine is the active, demethylated metabolite of venlafaxine.

Side effects of venlafaxine and desvenlafaxine

- Are nausea, headache, sexual dysfunction, dizziness, insomnia, Sedation, and constipation.
- Increase in blood pressure and heart rate (at high doses)

Duloxetine

- It is a moderate inhibitor of CYP2D6 isoenzymes (Increase concentrations antipsychotics)
- Metabolized in the liver to inactive metabolites (Avoided in patients with liver dysfunction).

Side effects of duloxetine

- Nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, sweating, and sexual dysfunction, may increase blood pressure or Heart rate.

Atypical antidepressants
Bupropion
Mirtazapine
Trazodone
Vilazodone
Vortioxetine

Bupropion

- Bupropion is a weak dopamine and norepinephrine reuptake inhibitor
- That is used to alleviate the symptoms of depression.
- Bupropion is also useful for decreasing withdrawal symptoms in patients trying to quit smoking.

Side effects of bupropion

- Dry mouth, sweating, nervousness, tremor, seizures (dose dependent)
- Sexual dysfunction (very low incidence).

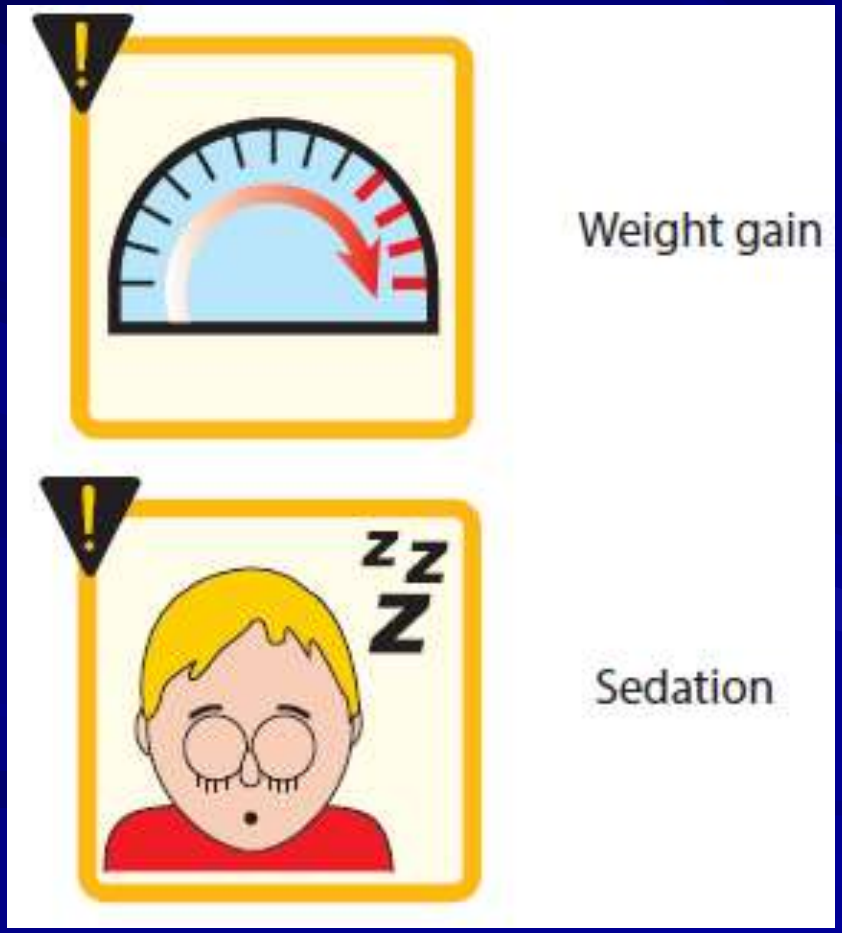
Mirtazapine

- Mirtazapine enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at presynaptic α2 receptors.
- Antagonism at 5-HT2 receptors
- Antihistaminic activity(sedation may be an advantage in depressed patients having difficulty sleeping.

Side Effect of Mirtazapine

1. Increased appetite & weight gain
2. Sedation

Some commonly observed adverse effects of mirtazapine.



Tricyclic Antidepressants Tcas
Mechanism of Action

1. Inhibition of neurotransmitter reuptake:
   - TCAs and amoxapine are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals.
   - Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake.
2. Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. Amoxapine also blocks 5-HT2 and dopamine D2 receptors.

Therapeutic Uses

1. Depression (moderate to severe)
2. Panic disorder (some patients respond toTCAs).
3. Imipramine has been used to control bed-wetting in children older than 6 years of age; however, it has largely been replaced by desmopressin
4. Prevent migraine headache and treat chronic pain syndromes (The TCAs, particularly amitriptyline)
5. Insomnia (low doses of TCAs, especially doxepin)

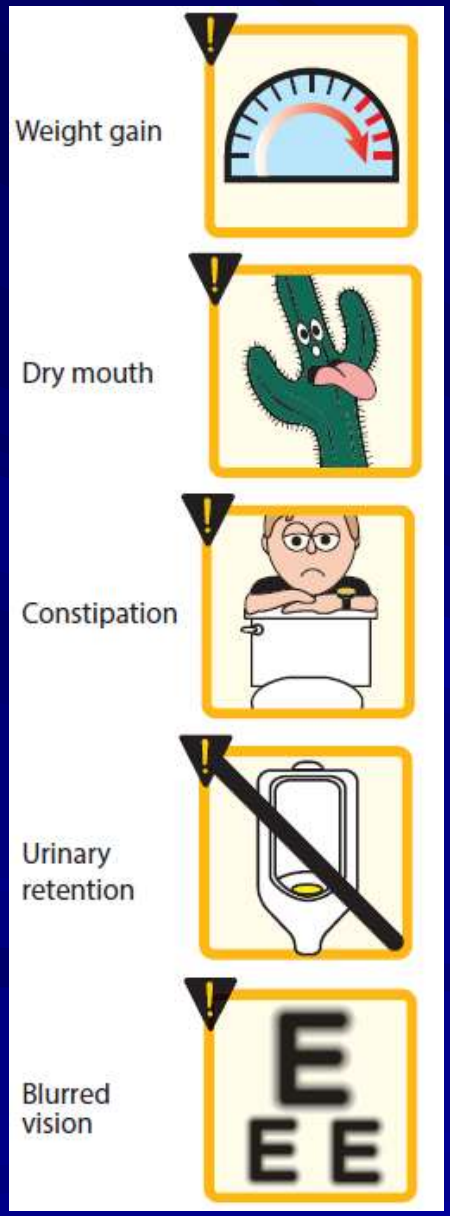
Pharmacokinetics

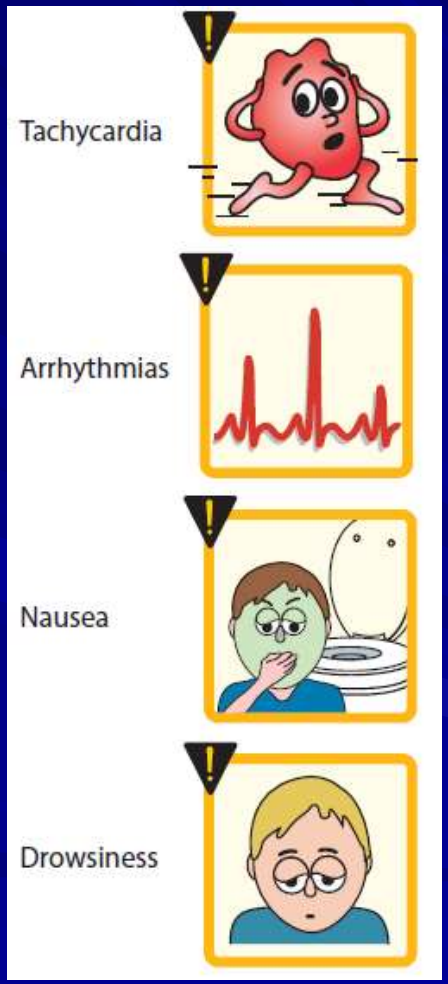
- Well absorbed after oral administration.
- Widely distributed and readily penetrate into the CNS (lipophilic nature).
- Metabolized by the hepatic microsomal system
- Conjugated with glucuronic acid.
- Excreted as inactive metabolites by the kidney.

Adverse Effects

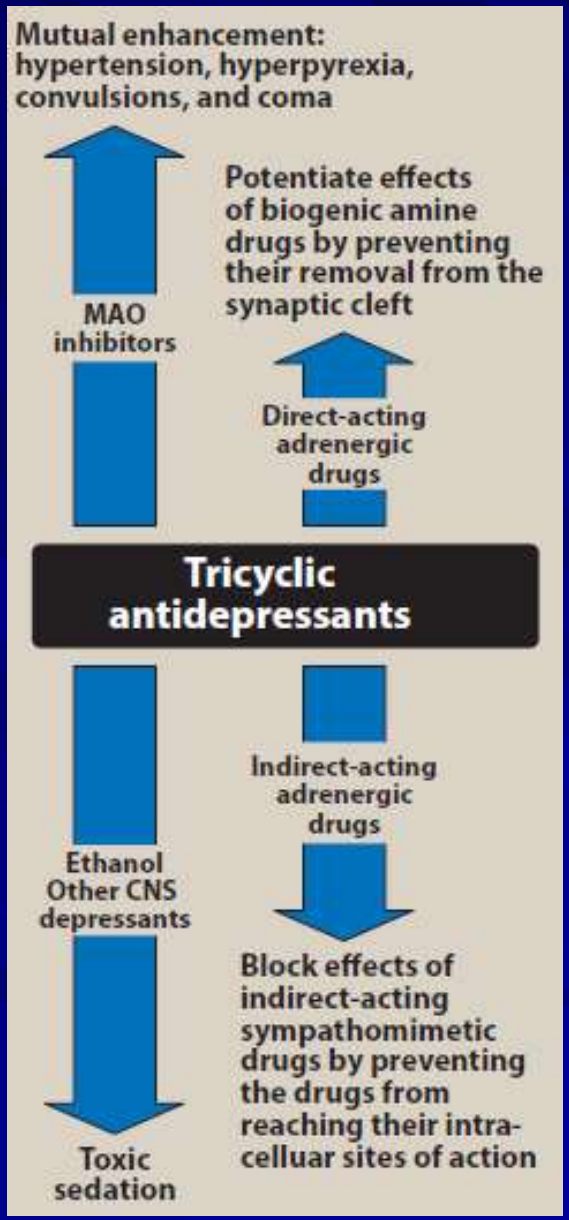
1. Antimuscarinic Adveres Effects (Blurred Vision, Xerostomia ,Urinary Retention, Sinus Tachycardia, Constipation, Glaucoma)
2. Life-threatening Arrhythmias (Overdose).
3. Orthostatic Hypotension, Dizziness&reflex Tachycardia (Duo To Block A-adrenenrgic Receptors(imipramine Is The Most Likely)
4. Sedation(especially During The First Several Weeks Of Treatment,
5. Duo To Block Histamine H1 Receptors.
6. Weight Gain
7. Sexual Dysfunction (Lower Than That Associated With The Ssris).

Observed adverse effects of tricyclic antidepressants.





Drugs interacting with tricyclic antidepressants.



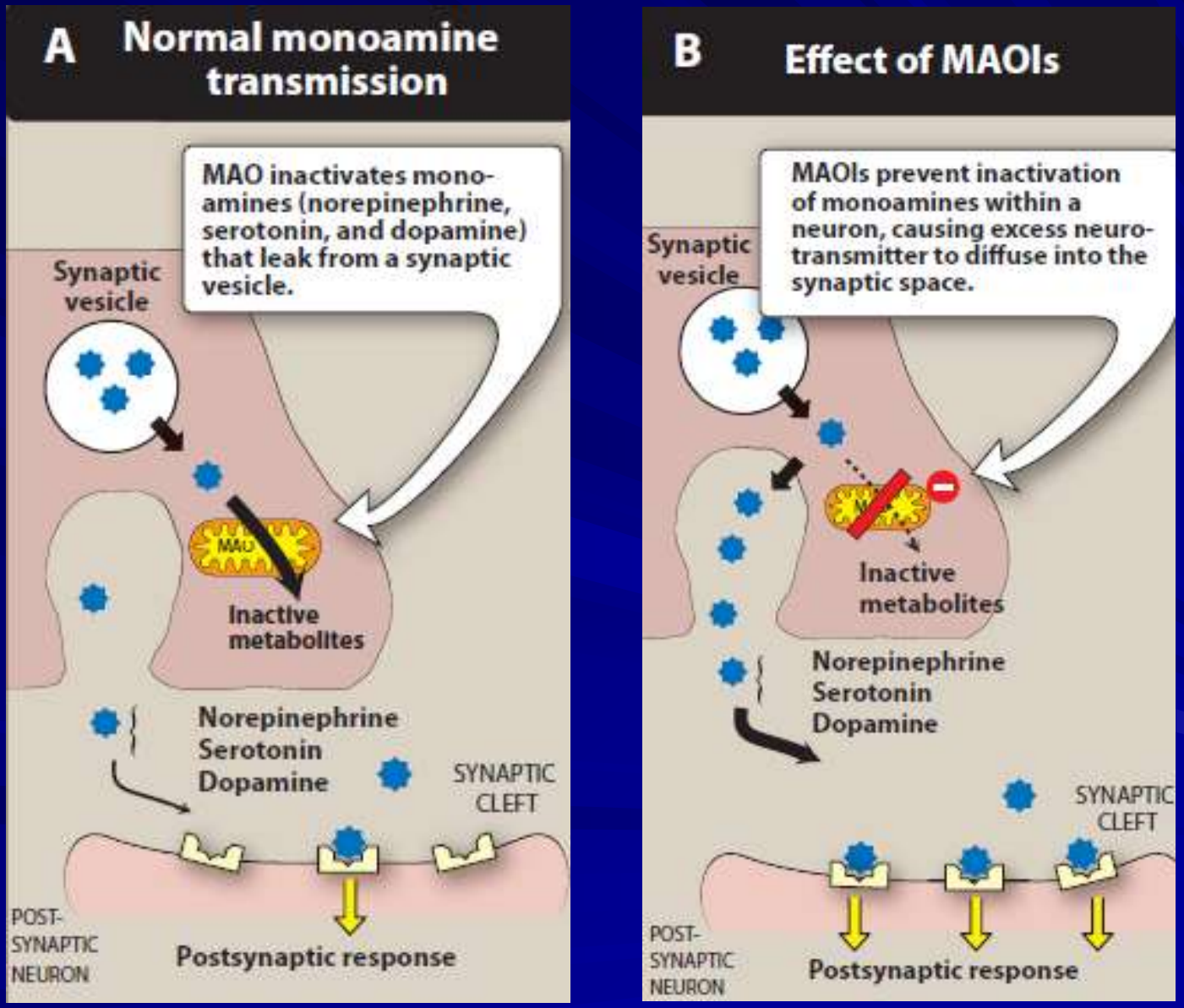
Phenelzine
Tranylcypromine
Isocarboxazid
Selegiline (The only antidepressant available in a transdermal delivery system)

- Use of MAOIs is limited due to the complicated dietary restrictions required while taking these agents.

- MAOIs may irreversibly or reversibly inactivate the enzyme, permitting Neurotransmitters to accumulate within the presynaptic neuron and leak into the synaptic space.

Note: Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron

Mechanism of action of monoamine oxidase inhibitors (MAOIs).



Therapeutic Uses of MAOIs

- The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.
- Atypical depression

Note: Drug-drug and drug-food interactions, limit the widespread use of MAOIs

Pharmacokinetics of MAOIs

- These drugs are well absorbed after oral administration.
- A minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant (Enzyme regeneration, when irreversibly inactivated usually occurs several weeks after termination of the drug)
- MAOIs are hepatically metabolized and excreted rapidly in urine.

Adverse effects of MAOIs

- Drug-food and drug-drug interactions , tyramine, which is contained in foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut.
- Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet.
- Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, stroke

- Drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.
- Due to the risk of serotonin syndrome, the use of MAOIs
  with other antidepressants is contraindicated. For example, SSRIs Should not be coadministered with MAOIs. Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of fluoxetine, which should be discontinued at least 6 weeks before a MAOI is initiated.